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| 09/815,577 | 03/23/2001 | Brittan L. Pasloske | AMBI:054US/MBW | 7249 |

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|---|---|
| CRANE, LAWRENCE E | |
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| 1623 | |

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Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. 09/815,577 | Applicant(s) Pasloske et al. | |
|---|---|---|---|
| | Examiner L. E. Crane | Group Art Unit 1623 | |

***- THE MAILING DATE of this communication appears on the cover sheet beneath the correspondence address -***

## Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE --3-- MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be filed after six months from the date of this communication.
- If the prior for reply specified above is less that thirty (30) days, a reply within the statutory minimum of thirty days will be considered timely.
- If NO period for reply is specified above, such period shall ,by default, expire SIX (6) MONTHS from the date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 USC §133).

## Status

[X] Responsive to communication(s) filed on -03/23/01 (amdt A)-.
[] This action is **FINAL.**
[] Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle,* 1935 C.D. 11; 453 O.G. 213.

## Disposition of Claims

[X] Claims --54-87-- are pending in the application. Claims -1-53- have been cancelled.
Of the above claim(s) --[]-- is/are withdrawn from consideration.
[] Claim(s) --[]-- is/are allowed.
[X] Claims --54-87-- are rejected.
[] Claim(s) --[]-- is/are objected to.
[] Claim(s) --[]-- are subject to restriction or election requirement.

## Application Papers

[] See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
[X] The proposed drawings, filed on -03/23/01- are [X] approved [] disapproved.
[] The drawing(s) filed on -[]- is/are objected to by the Examiner.
[] The specification is objected to by the Examiner.
[] The oath or declaration is objected to by the Examiner.

## Priority under 35 U.S.C. § 119(a)-(d)

[X] Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119 (a)-(d).
[X] All [] Some* [] None of the CERTIFIED copies of the priority documents have been
[] received.
[] received in Application No. (Series Code/Serial Number) -[]-.
[X] received in the national stage application from the International Bureau (PCT Rule 17.2(a)).
* Certified copies not received: -[]-.

## Attachment(s)

[] Information Disclosure Statement(s), PTO-1449, Paper No(s). --[]--
[X] Notice of Reference(s) Cited, PTO-892
[] Notice of Draftsperson's Patent Drawing Review, PTO-948
[] Interview Summary, PTO-413
[] Notice of Informal Patent Application, PTO-152
[] Other: -[]-.

Claims **1-53** have been cancelled and new claims **54-87** have been added as per the preliminary amendment filed March 23, 2001.

Claims **54-87** remain in the case.

The non-statutory double patenting rejection, whether of the obviousness-type or non-obviousness-type, is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent. *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969); *In re Vogel,* 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Van Ornam,* 686 F. 2d 937, 214 USPQ 761 (CCPA 1982); *In re Longi,* 759 F.2d 887, 225 USPQ 645 (Fed. Cir 1985); and *In re Goodman,* 29 USPQ 2d 2010 (Fed. Cir. 1993).

A timely filed terminal disclaimer in compliance with 37 C.F.R. § 1.321(b) and (c) may be used to overcome an actual or provisional rejection based on a non-statutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 C.F.R. §1.78(d).

Effective January 1, 1994, a registered attorney or agent or record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 C.F.R. §3.73(b).

Claims **54-57 and 61-72** are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims **1-25 and 32-44** of copending Application No. **09/160,284**. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims may be read to be directed to the deactivation of ribonuclease enzymatic

activity by contacting a sample thought to be contaminated with ribonuclease with a disulfide-forming reducing agent.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims **54-60, 69-78, 80-83 and 85-86** are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

In the instant disclosure and in claims not listed in this rejection (e.g. claims **61-68**) applicant has listed specific reducing agents limited to thiol (-SH) containing compounds and in independent claims has relied on the term "reducing agent." The compounds which are not thiol containing agents but are "reducing agents" and which are not enabled herein is substantial. Therefore, the instant written description fails to provide adequate support for the breadth of claims wherein the non-thiol reducing agents are included. Limitation to thiol containing reducing agents is respectfully requested.

Claim **87** is rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Claim **87** by its failure to specify any "reducing agent" is not enabled by any written description within the instant disclosure.

Claims **54-79** are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

In claims **54-79** there is an implicit assumption that the mixture of an RNAse and RNA can be treated with a chemical reducing agent and that said reagent will selectively act on the RNAse without interference from the RNA present. Applicant is referred to PTO-892 reference "**W**" (**Murthy et al.**) at p. 347, column 1, first full paragraph, wherein it is stated that " .. the presence of RNA during [DTT] pretreatment [of the enzyme] was found to resist such a change, implying substrate stabilization of the RNAse BS-1 in the dimeric state with lower inhibitor-sensitivity, or insensitivity to it." In the same reference at p. 344, column 2, the 10 lines above Figure 1 disclose that DTT is mixed with an RNAse/RNA mixture at 37 degrees. And in Figures 4 and 5, the influence of the concentration of RNA on RNAse inactivation is disclosed. Because the instant disclosure does not appear to present a clear and cogent explanation of how applicant's have overcome the problem of inhibitor induced RNAse insensitivity to a thiol reducing agent disclosed in the noted prior art disclosure, examiner concludes that the instant claims are at a minimum lacking in enablement for exemplifications wherein as noted in Murthy et al. the inhibitor has no effect on the enzyme because of the interaction of the enzyme with the RNA substrate. In addition, the disclosure of Murthy et al. at p. 345, Figure 3, and associated explanatory text teaches that the RNAse "BS-1" retains some to all of its enzymatic activity after reduction of the RNAse with DTT at 37°C either in the presence of an RNAse inhibitor or in the absence thereof. Therefore, it is clear that applicant's generic claims wherein the specific

RNAse's to be inactivated have not been specified lack proper enabling support; i.e. not all RNAse's are effectively inhibited by the reducing agents of the instant claimed process. Therefore, in light of the Murthy et al. disclosure, applicant is respectfully requested to limit the scope of the instant claims to the specific embodiments.

Furthermore, the disclosure of the **Khesin et al.** reference (PTO-892 ref. **Y**) directly contradicts the assumption that the action of reducing agents including "DTT" and the like on ribonucleases always reduces ribonuclease activity, suggesting that limitations on claim scope are essential in order to take this reference into account.

Claims **54-58, 61-72, 74-76, 81 and 86-87** are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim **54**, the term "method comprising" is incomplete because the purpose of the method has not been supplied; i.e. the claim begs the question "method of doing what?". See also claims **55-57 and 61-72**.

In claims **55 and 74**, the term "is further defined as comprising" is apparently intended to alert the reader of the claim that additional subject matter is being added to the subject matter of the claim depended from. If this was applicant's intended meaning, applicant is respectfully requested to substitute the standard term of art (-- further comprising --) used for this purpose in place of the noted term. See claims **59-60, 77-78, 82-83 and 85-86** as examples wherein the term -- further comprising -- has been used correctly. Similar problems also occur in claims **56-58, 74-76 and 81**.

Claim **81** is improperly dependent because the subject matter of claim **80** has not been further limited.

In claims **86 and 87** the term "Armored RNA®" is a registered trademark and its association with any particular chemical substance may therefore be altered at the whim of the owner of the trademark. For this reason the noted term is not permissible subject matter for a patent claim and therefore, its deletion or replacement with complete chemical structure/identity information describing the substance implied by the noted term is respectfully requested.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. §102 that form the basis for the rejections under this section made in this Office action:

> "A person shall be entitled to a patent unless -
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent."
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States."

Claims **80-85** rejected under 35 U.S.C. §102(**b**) as being anticipated by **Murthy et al.** (PTO-892 ref. **W**).

Applicant is referred to PTO-892 reference "**W**" (Murthy et al.) at p. 347, column 1, firs full paragraph, wherein it is stated that " .. the presence of RNA during [DTT] pretreatment [of the enzyme] was found to resist such a change, implying substrate stabilization of the RNAse BS-1 in the dimeric state with lower inhibitor-sensitivity, or insensitivity to it." In the same reference at p. 344, column 2, the 10 lines above Figure

1 disclose that DTT is mixed with an RNAse/RNA mixture at 37 degrees. Because applicant has failed to define the chemical identity or structural modification information necessary to distinguish RNA from "Armored RNA®," examiner assumes that all of the RNA present is unmodified. Applicant is also requested to note that "acetate" and "DTT" are both nominally "chelators," thereby meeting the limitation of claim **31** without more.

The following is a quotation of 35 U.S.C. §103(**a**) which forms the basis for all obviousness rejections set forth in this Office action:

> "A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made."

Claims **54-57 and 61-72** are rejected under 35 U.S.C. §103(**a**) as being unpatentable over **Murthy et al.** (PTO-892 ref. **W**) in view of **Boshes et al.** (PTO-892 ref. **U**) and further in view of **Cleland** (PTO-892 ref. **V**).

The instant claims are directed to all processes wherein cells or extracts thereof are contacted with a reducing agent and an undefined level of heating, or optionally one of two defined levels of heating, are applied.

**Murthy et al.** at column 2 of p. 344 immediately preceding Figure 1 describes the treatment of an RNAse with dithiothreitol at 37°C.

**Boshes et al.** at page 485, at the bottom of column 2, discloses that DTT and ß-mercaptoethanol are both capable of reducing an RNAse.

**Cleland** discloses in its abstract and at page 480, column 1 et seq, that there are numerous reducing agents with substantial equivalence to DTT, including DET, cysteine, and ß-mercaptoethanol.

The substitution of another disulfide-formation-capable reducing agent for DTT in the **Murthy et al.** process, as motivated by the Boshes et al. reference, is deemed to be a variation on the Murthy et al. process which would have been within the purview of the ordinary practitioner seeking to optimize the Murthy process by selecting any one of the alternative reducing agents disclosed in the Boshes and Cleland references. The repetition of such a process as warranted is deemed to be a variation of the prior art specifically motivated by the variation in experimental conditions taught at p. 345, column 2, line 4 et seq of Murthy et al., and which is therefore clearly within the purview of the ordinary practitioner seeking to minimize RNAse activity in RNA samples. For these reasons the instant claimed process is deemed to lack patentability in view of the noted prior art.

Therefore, the instant claimed method of stabilizing mixtures of RNA and RNAse's by contacting same with a reducing agent like DTT would have been obvious to one of ordinary skill in the art having the above cited references before him at the time the invention was made.

Claims **54-86** are rejected under 35 U.S.C. §103(**a**) as being unpatentable over **Murthy et al., Boshes et al.** and **Cleland** in view of **Chomczynski '515** (PTO-892 ref. **B**) and further in view of **Pasloske et al.** (PTO-892 ref. **C**).

The instant claims are directed to methods of isolating cDNA wherein a reducing agent is present in the isolation steps to inhibit ribonuclease activity and optionally wherein the product RNA or DNA

are further processed in a reverse transcriptase-based polymerase chain reaction (PCR) process to increase the quantity of nucleic acid isolated.

**The Murthy et al., Boshes et al.** and **Cleland** references are described in the previous rejection.

**Chomczynski '515** is directed to is isolation of RNA and DNA from tissues using standard solution lysis conditions including a reducing thiol (see column 6 at line 46). In addition, **Chomczynski** at column 7 lines 1-4 and lines 65-68 and at column 8 lines 1-9 teaches the use of polymerase chain reaction (PCR) relying on reverse transcriptase (RT-PCR) which uses the RNA and DNA produced by said isolation process.

The use of a reducing agent by **Chomczynski '515** is specified at column 4, line 24, thereby motivating the ordinary practitioner to elect alternatives to the thiol amine used by this reference as part of a modified isolation procedure devised to improve on the prior art in the course of routine experimentation. The modification of **Chomczynski '515** by substitution of alternative reducing agents as disclosed in the secondary references is therefore clearly motivated by the primary '515 reference.

The substitution of an alternative reducing agent into the process of **Chomczynski** would have been an obvious variation to the ordinary practitioner in view of the guidance of this reference as noted above.

Therefore, the instant claimed method of stabilizing mixtures of RNA by inhibition of RNAse's by contacting same with a reducing agent like DTT during the process of isolation of the RNA would have been obvious to one of ordinary skill in the art having the above cited references before him at the time the invention was made.

Claim **87** is rejected under 35 U.S.C. §103(**a**) as being unpatentable over **Pasloske et al.** (PTO-892 ref. **C**) in view of **Mulder et al.** (PTO-892 ref. **TA**).

The instant kit is apparently directed to materials required for the production of a cDNA sample by reverse-transcriptase-based polymerase chain reaction (RT-PCR).

Applicant is referred to the **Pasloske et al. '262** reference at column 24 beginning at line 9 through column 26 wherein the component parts of the instant claimed kit are effectively disclosed by invocation of the term "RT-PCR" and further includes encapsulated RNA, aka "Armored RNA™." See also reference to Mulder et al. at column 22, line 13.

The **Mulder et al.** reference is directed to the process of RT-PCR™. At page 292, column 2, at lines 20-22 discloses the lysis buffer used for nucleic acid release from plasma. Mulder also discloses at page 293 column 1, last three lines though column 2, line 6 many of the components of the "kit" claimed herein including Tth DNA polymerase, RNA polymerase, RNase-free DNase and the well known RNase inhibitor diethyl pyrocarbonate. Additionally at page 293, column 2, at mid-column the reverse transcription buffer/RT and dNTP's are disclosed

Claims directed to a multiple component kit useful for practicing RT-PCR™ wherein some of the components are disclosed in the primary reference and specific reference is made to the secondary reference clearly motivates the selection of the Mulder RT-PCT protocol combined with the Armored RNA of Pasloske et al. to generate a kit useful in the Pasloske process for production of cDNA.

Therefore, the instant claimed kit for producing cDNA would have been obvious to one of ordinary skill in the art having the above cited references before him at the time the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. §103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. §1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. §103(c) and potential 35 U.S.C. §§102(f) or (g) prior art under 35 U.S.C. §103(a).

Papers related to this application may be submitted to Group 1600 via facsimile transmission(FAX). The transmission of such papers must conform with the notice published in the Official Gazette (1096 OG 30, November 15, 1989). The telephone numbers for the FAX machines operated by Group 1600 are **(703) 308-4556** and **703-305-3592**.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner L. E. Crane whose telephone number is 703-**308-4639**. The examiner can normally be reached between 9:30 AM and 5:00 PM, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. Gary Geist, can be reached at (703)-308-1701.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1600 receptionist whose telephone number is 703-**308-1235**.

LECrane:lec
**11/19/01**

L. Eric Crane
Patent Examiner
Group 1600